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Secondary Hemochromatosis as a Long-Term Complication of the Treatment of Hematologic Malignancies

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The increased cure rate of hematologic malignancies including the use of bone marrow transplantation has focused attention on the chronic toxicity and quality of life of the survivors. We have observed five patients who have been diagnosed with clinically significant iron overload, presumably due to packed red blood cell transfusions, ≥12 months after transplant for a hematologic malignancy. In these patients, there is no history of veno-occlusive disease or family history of hemochromatosis. The allotransplant patient has been free of chronic graft versus host disease. Family screening has been negative. No patient developed clinically significant endocrinopathy, arthropathy, or cardiac disease. The patients have been treated with phlebotomy to bring the transferrin saturation and ferritin levels to normal. The long-term follow-up of patients treated for a hematologic malignancy should include analysis of hepatitis C virus and iron status. This may prevent the development of clinically significant chronic liver disease and possibly malignancy. Am. J. Hematol. 61:262–264, 1999.

Key words: hemochromatosis; leukemia; bone marrow transplantation

INTRODUCTION

The increased cure rate of hematologic malignancies including the use of bone marrow transplantation has focused attention on the chronic toxicity and quality of life of the survivors. This is a report of five patients who were found to have iron overload at least one year after the completion of therapy. Iron deposition may be a cause of clinically significant hepatic dysfunction and long term morbidity. We believe it is an under reported, long term problem of therapy.

PATIENTS AND METHODS

Five patients who had been treated for hematological malignancies between May 1988 and June 1991 were found to have abnormally elevated ferritin levels (Table 1). Liver biopsies were obtained in 2 patients and were diagnostic of hemochromatosis. In these patients there was no history of venoocclusive disease or family history of hemochromatosis. The one allogeneic bone marrow transplant patient has been free of chronic graft versus host disease. Patients are being treated with phlebotomy to return the transferrin saturation and ferritin levels to normal. All patients have been in remission since the completion of the bone marrow transplantation procedure.

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TABLE I. Patient Information*

Age	Diag	BMT	Time	PRBC	%Sat	Ferritin	HCV	Biopsy	HLA A3
22/M	AML	AUTO	22/84	na	78	5000	pos	pos	pos
37/M	AML	ALLO	27/60	52	20	1439	nd	nd	nd
30/M	HD	AUTO	23/12	44	54	1147	pos	nd	nd
37/M	AML	AUTO	24/12	66	100	9942	nd	pos	pos
21/F	HD	AUTO	84/36	30	—	3239	neg	nd	nd

*Age = age at original diagnosis; Biopsy pos indicates diagnostic of hemochromatosis; HCV = hepatitis C virus antibody; %Sat = transferrin saturation; ferritin ng/ml; nd = not done; BMT = bone marrow transplant; Time = months from diagnosis to BMT/ months from BMT to diagnosis of iron overload; PRBC = units of packed red blood cells received for all therapy.

DISCUSSION

An increasing number of patients are long term survivors of hematologic malignancies, often after a successful treatment, sometimes including bone marrow transplantation [1]. These patients have been transfused with many units of iron containing packed red blood cells. In one study of 118 patients treated for acute myelogenous leukemia, a median of 18 (range 3–44) units of red blood cells were transfused [2]. Patients receive additional red blood cells during the transplant period [3]. In childhood acute lymphocytic leukemia, the serum ferritin level correlated with the amount of red blood cells transfused. The data suggested that children who receive intensive chemotherapy have excessive stores of iron, that the extent of iron overload is correlated with the amount of red blood cells transfused, and that this iron overload may lessen over time [4]. This excessive iron may be a cause of chronic morbidity. High serum iron levels are often found in chronic carriers of hepatitis C (HCV). HCV can lead to chronic hepatitis, cirrhosis, and hepatocellular carcinoma [5,6]. The potential for liver injury is increased if this infection is associated with iron overload. HCV had been frequently seen in bone marrow transplant recipients [7].

Hemochromatosis is a disorder of excess iron overload that can lead to organ damage from the accumulation of ferritin and hemosiderin in hepatocytes. It can be caused by several genetic causes including hereditary hemochromatosis and thalassemia major, or may be acquired from chronic ingestion of medicinal iron, transfusional iron overload, acquired sideroblastic anemia, and porphyria cutanea tarda [8,9]. Hereditary hemochromatosis (HH) is inherited in an autosomal recessive pattern, on the short arm of chromosome 6. There is an association with HLA-A3 and B7 antigen in HH patients [8].

Hepatic abnormalities in association with iron overload have been reported in bone marrow transplantation [10]. It was shown that 88% of 1 year bone marrow transplant survivors had elevated ferritin levels. Patients received a median of 48 units of red blood cells for allo-bone marrow transplant patients and 53 units for auto-bone marrow transplant during the course of all treatments. Infection with HCV was found in approximately half of the patients. This study did not include liver biopsy nor reported any HLA information [10].

In our study, iron overload developed after completion of therapy as evidenced by an increased ferritin. These patients were identified at least 1 year after the transplant. Patients may have elevated ferritins in the immediate post-transplant period from causes other than iron overload. The patient who was HLA A3+ had the highest ferritin, albeit with the most packed red blood cells transfusions. This may indicate that this patient may also have HH as an associated condition and, therefore, increased susceptibility to iron overload.

Decreasing body iron stores may decrease the risk of chronic liver disease. We recommend that after bone marrow transplantation, patients be screened with serum ferritin and transferrin saturation. If clinically significant iron overload is found, patients should undergo liver biopsy. This may be particularly important in patients who have a HH associated HLA type. Phlebotomy therapy should be instituted to decrease risk of chronic liver disease and possibly primary hepatocellular carcinoma.

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